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Is Time the Missing Component in Protective Ventilation Strategies?

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Critical care physicians and intensivists are acutely aware that the mechanical ventilator, which is essential to keep their patient with acute respiratory distress syndrome (ARDS) alive, may also be the instrument of their death. The negative impact on pulmonary physiology of high airway pressures during mechanical ventilation has been known for over 4 decades (1). In 1974, Webb and Tierney were the first to show that mechanical ventilation could cause severe lung injury in rats (1). In addition, that seminal article also showed that increasing positive end-expiratory pressure reduced pulmonary edema and suggested that reduced tidal volumes (V_t) may decrease lung injury. Much has been learned about the pathophysiology of ventilator-induced lung injury (VILI) over the subsequent 40 years, but we are still uncertain of the optimal ventilator strategy to reduce ARDS morbidity and mortality (2).

The 2000 *New England Journal of Medicine* publication by the ARDSNetwork group was the first phase III clinical trial to show a statistically significant reduction in ARDS mortality secondary to lowering the V_t (3). Although that study led to initial excitement, recent publications have shown that even with low V_t ventilation the mortality from ARDS has not been reduced and remains near 40% (4–6). Clearly, we do not understand all of the important components within the mechanical breath, which are necessary to prevent VILI or even prevent the syndrome itself.

In this issue of *Critical Care Medicine* Silva et al (7) investigated the impact of various recruitment maneuver (RM) strategies on pulmonary epithelial and endothelial cell injury in a rat model of primary and secondary endotoxin-induced ARDS. The RM strategies all targeted a peak pressure of 30 cm H₂O and consisted of continuous positive airway pressure for 30 seconds (CPAP 30), stepwise increase in CPAP over 51 seconds (CPAP 51), and stepwise increase in CPAP over 30 seconds and held for another 30 seconds (CPAP 30/30). Their results showed that all RMs improved respiratory mechanics (i.e., elastance), but the impact on the molecular and cellular lung components varied with RM strategy. CPAP 30 with a very rapid application of pressure caused a significant reduction in surfactant protein B and higher levels of type III procollagen expression compared with CPAP 30/30. Although both RMs caused endothelial injury, the authors concluded that "...stepwise RM without sustained airway pressure appeared to associate with less biological impact on the lungs."

Because the airway pressure was identical in all RMs, what was the component in the mechanical breath that resulted in reduced lung injury? The answer, of course, is the "rate" and the "time" that the airway pressure is applied. Discussions of VILI mechanisms, either during ventilation or with RMs, usually focus on airway pressures (i.e., plateau pressure and positive end-expiratory pressure) and lung volumes (i.e., V_t) exclusively. Silva et al (7) address the extremely important concept of whole breath analysis, which identifies all components (i.e., rate, time, and pressure) of the mechanical breath that may impact the lung at the alveolar level. The term that they used to describe the whole breath analysis is the *pressure-time product* suggesting that "time" is equally as important as "pressure" when it comes to ventilator injury of the lung. Their data show that if the rate of gas delivery is reduced and the time at peak pressure is extended, lung injury can be reduced.

It is true that the differences in lung injury with the different RM strategies were moderate in the study by Silva et al, but we must remember that these differences were seen after a single RM. What if instead of a single RM we extended the pressure-time product as a ventilating strategy applied to these same animals over a period of hours? Obviously, the injury could be very severe. Our group has also been investigating whole breath analysis, focusing on the role of the "time" that airway pressure is applied on lung pathophysiology (8).

We hypothesized that if we applied a mechanical breath with an extended period of time at peak inspiration preemptively, before the development of lung injury, we could then prevent the development of ARDS (8). To analyze the whole breath, we developed an algorithm that takes into account both the time and the pressure at both inspiration and expiration, which we termed the *pressure/time profile* (P/T_P). Our analysis demonstrated that preemptive application of a mechanical breath strategy with a high P/T_P could prevent ARDS development (8).

The study by Silva et al demonstrates that the next phase in understanding the mechanisms of VILI will be analysis of the whole breath, not just pressures and volumes. It is no longer sufficient to simply analyze the pressures and volumes of the mechanical breath, but rather we must consider the rate of inspiration and expiration, the tidal volume and the functional

residual capacity, the flow velocity during inspiration and expiration, and finally the airway pressures and the time that these pressures are applied during both inspiration and expiration. We need to go beyond the assumption that the macroventilatory parameters are the key drivers of lung pathophysiology in a fashion similar to the evolution in the understanding of hemorrhagic shock resuscitation. Initially, shock pathophysiology was believed due only to the macrocirculatory changes, whereas we now know that the critical mechanistic component in shock pathophysiology occurs in the microcirculation.

In the lung, we need to go beyond the macroparameters displayed on the ventilator screen and determine the impact of the pressures, times, rates, and volumes of the gas being delivered at the microventilatory level. Once we have a thorough comprehension of how all the components of the mechanical breath impact the lung at the alveolar level, we will begin to understand the true mechanisms of VILI.

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